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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,041	02/14/2002	Hideki Ishihara	0397-0440P	6640

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,041	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *9/15/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10* is/are pending in the application.

4a) Of the above claim(s) *7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed September 15, 2005 in response to the Office Action of May 31, 2005, is acknowledged and has been entered. Applicant's reaffirmation of the election of Group I, claims 1-7, and the species of CDK1 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)). Previously pending claims 1, 2, 6, and 7 have been amended, claims 8 and 9 were canceled, and claim 10 was added. Claims 1-6 and 10 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

3. Claim 1, 2, 3, 6 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (*J Biol Chem*, 1993, Vol. 268: 20443-20451) in view of Blain et al (Journal of Biological Chemistry, 1997, 272:25863-25872), Jeong and Nikiforv (*BioTechniques*, 1999, Vol. 27: 1232-1238, IDS), and Facemyer and Cremo (*Bioconjug Chem*, 1992, Vol 3: 408-413, IDS).

Claims 1, 2, 3, 6 and 10 are drawn to a method for calculating the activity of a cyclin-dependent kinase comprising catching the cyclin-dependent kinase by an anti-cyclin-dependent kinase antibody, reacting ATP-γS with a substrate (that does not contain a sulfur atom) for a CDK, labeling the substrate with a fluorophore, removing excess label or enzyme not labeled, measuring the fluorescence from the label in the product, calculating the activity of the CDK from the measured amount of label in the product with reference to a pre-produced curve (claims 1 and 10), CDK1 (claim 2), fluorescent dye (claim 3), a histone H1 substrate (claim 6), and a method for obtaining the activity of a cyclin-dependent kinase comprising catching the cyclin-dependent kinase by an anti-cyclin-dependent kinase antibody, reacting ATP-γS with a substrate (that does not contain a sulfur atom) for a CDK, labeling the substrate with a fluorophore, removing excess label or enzyme not labeled, measuring the fluorescence from the label in the product, and obtaining the activity of the CDK from the measured amount of label in the product (claim 10).

Pan et al. teach a method for calculating or obtaining the activity of cdc2 (CDK1) comprising incubating a CDK1/cyclin complex with [γ-^{32}]ATP and histone H1 and measuring CDK1 phosphorylation activity by quantifying [^{32}P] in the product and comparing it to control measurements (page 20444). Pan et al. does not teach reacting ATP-γS with a substrate, catching CDK with an antibody, labeling the substrate with a fluorophore, removing excess label, and calculating the fluorescence from a labeled substrate.

Blain et al teach catching a cyclin-dependent kinase using an anti-cyclin-dependent kinase antibody (immunoprecipitation) for a kinase assay (p. 25864, col. 1).

Jeong and Nikiforv (herein referred to as "Jeong") teach a non-radioactive method of calculating protein kinase activity comprising reacting ATP-γS with a substrate, kemptide (which does not naturally contain a thiol group or sulfur atom), to create a thiophosphorylated product (page 1232, column 3) and measuring fluorescence values in the final product (page 1233, columns 1 and 2). The reference teaches the conventional wash step of removing excess label (p. 1232, col. 2). The reference teaches that the biggest drawback of the present method is the relatively slow rate of the biotinylation step, however this can be overcome by various methods and thus it represents a viable alternative to existing methods of screening protein kinases (page 1238, column 2). The reference suggests this method is useful for a wide range of different kinases (page 1232, third column). Further, the reference teaches that presented is an alternative approach for detecting kinase activity wherein the method does not require the use of radioactivity and allows flexibility in the detection scheme (p.1238, column 2).

Facemyer and Cremo teach a method of using a protein kinase and ATP-γS to create a thiophosphorylated protein and the method of labeling a thiophosphorylated protein by coupling the sulfur of the protein phosphorothioate to a fluorescent haloacetate (page 409). It is noted that the reference further teaches that thiol groups in the substrate are blocked prior to reaction with ATP-γS (See Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the methods of Blain et al and Jeong for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate because Blain et al teach the conventionally used method of catching a cyclin-dependent kinase with an antibody for a kinase assay and Jeong specifically teach the disadvantages of traditional assays of enzyme activity of protein kinases which use [γ-^{32}]ATP which require radioactivity and multiple steps. One would have been motivated to substitute the methods of Blain et al and Jeong for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate in order isolate the cyclin-dependent kinase from the cell sample to reduce artifacts from other CDKs and to eliminate the disadvantages specifically taught by Jeong, and because Jeong specifically suggest that the method is useful for a wide range of different kinases. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to substitute the direct fluorescent labeling of the thiol of the reacted ATP-γS of Facemyer and Cremo for the labeling steps of the combined references because Jeong specifically teach that the biggest drawback of their method is the relatively slow rate of the biotinylation step. One would have been motivated to substitute the direct fluorescent labeling of the thiol of the reacted ATP-γS of the Facemyer and Cremo for the labeling steps of the combined references in order to save not only time, but also the cost of the labeling reagents of Jeong.

4. Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al., Jeong, and Facemyer and Cremo and in further view of Hemmila (*Clin. Chem.*, 1985, vol. 33, pages 359-370).

The claims are drawn to a method of determining the activity of a cell cycle regulatory factor comprising reacting ATP-γS with a substrate for a CDK, labeling the substrate with a fluorophore, measuring the fluorescence from the label in the product, calculating the activity of the CDK from the measured amount of label in the product with reference to a pre-produced curve (claim 1), and a fluorescent dye FITC (claim 4).

Pan et al., Jeong and Nikiforv, and Facemyer and Cremo teach as set forth above. However, the combined references do not specifically teach labeling the substrate with FITC.

Hemmila teaches several methods of fluoroimmunoassays (FIA) using FITC as a fluorescent label for substrates. The reference teaches that FITC is the probe most widely used in both immunofluorescence and FIA (page 361, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute FITC label as taught by Hemmila for the fluorescent labels used by Jeong and Nikiforv or Facemyer and Cremo in the combined references because FITC is a conventionally used fluorescent probe. One would have been motivated to substitute this label in the method of the combined references because the use of FITC was well known in the art as a commercially available label for proteins and offers a safe method for labeling and detecting specific proteins in a sample without the use of hazardous materials such as radioisotopes.

5. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al., Jeong, and Facemyer and Cremo, in further view of Strachan and Read (*Human Molecular Genetics*, 1999, BIOS Scientific Publishers Ltd., section 20.2.5).

The claims are drawn to a method of determining the activity of a cell cycle regulatory factor comprising reacting ATP-γS with a substrate for a CDK, labeling the substrate with a labeling enzyme, measuring the amount of label in the product, calculating the activity of the CDK from the measured amount of label in the product with reference to a pre-produced curve (claim 1), and a labeling enzyme peroxidase (claim 5).

Pan et al., Jeong and Nikiforv, and Facemyer and Cremo teach as set forth above. However, the references do not specifically teach labeling the substrate with a labeling enzyme peroxidase.

Strachan and Read teach the conventional use of a peroxidase enzyme as a protein label and detection system and teach that the system offers the use of readily available commercial affinity-purified secondary antibodies (pages 6 and 7 of 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the peroxidase label of Strachan and Read for the fluorescent labeling methods of Jeong and Nikiforv and Facemyer and Cremo in the method of the combined references because Strachan and Read teach that peroxidase is a conventional reporter molecule. One would have been motivated to substitute this method as a labeling and detection system for the substrate of the

combined references because the method of labeling the substrate with a peroxidase enzyme was well known in the art, conventional, and offers the use of readily commercial affinity-purified secondary antibodies, which is a safe method of labeling and detection without the use of hazardous materials such as radioisotopes.

6. Some of the Applicant's arguments are drawn to the rejection of claims 1, 2, 3, and 6 recited in the paper mailed September 15, 2005, pages 9-12, are relevant in the instant rejections.

Applicant argues that a *prima facie* case of obviousness has not been established. Applicant argues that the primary reference, Pan et al, fails to disclose or recognize catching CDK in a sample by an anti-CDK antibody, reacting ATP-γS with a substrate, labeling the substrate, with a fluorophore or enzyme, as well as measuring the fluorescence or enzyme from a labeled substrate. The argument has been considered but has not been found persuasive because Applicant is arguing the individual reference and the claims are rejected for the reasons previously set forth as drawn to the combined references.

Although Applicant argues that Pan et al, Jeong nor Facemyer and Cremo (herein referred to as "Facemyer") fail to teach a step for catching the CDK with an anti-CDK antibody and removing excess label, this argument is not found relevant in view of the new grounds of rejection.

Applicant argues that Facemyer does not teach cyclin-dependent kinase. The argument has been considered but has not been found persuasive because Applicant is

arguing the individual reference and the claims are rejected for the reasons previously set forth as drawn to the combined references.

Applicant argues that one of ordinary skill in the art would not have the requisite motivation to combine the disclosure of Pan and Jeong with that of Facemyer in order achieve the present invention because Facemyer does not even recognize the nature of the problem to be solved nor does the Facemyer reference describe cyclin-dependent kinase as instantly claimed. The argument has been considered but has not been found persuasive because, again, Applicant is arguing the individual references and is ignoring the teachings of the combined references. Although Facemyer does not describe cyclin-dependent kinase Pan et al does, in fact, describe cyclin-dependent kinase, Jeong teaches a method that is useful for a wide range of kinases, and Facemyer is used only to reiterate the conventional use of ATP-γS in kinase assays as well as the conventional use of fluorescent labels in these assays. The fact that Facemyer, alone, is not drawn to the claimed invention is irrelevant.

Applicant argues that the combined references are not a proper "obvious to try" rationale. The argument has been considered but has not been found persuasive because one of ordinary skill in the art would have a reasonable expectation of success because Jeong specifically teach that the method is useful for a wide range of kinases. Again, the Facemyer reference was used only to reiterate the conventional use of fluorescent labels with ATP-γS. Again, the fact that Facemyer lacks a disclosure of cyclin-dependent kinase is irrelevant given the teachings of the combined references.

7. Some of the Applicant's arguments are drawn to the rejection of claims 1 and 4 recited in the paper mailed September 15, 2005, pages 12-13, are relevant in the instant rejections.

Applicant argues that Hemmila fails to disclose catching CDK using an anti-CDK antibody, reacting ATP-γS with a substrate in the presence of CDK, and calculating the activity of CDK as instantly claimed, thus a *prima facie* case of obviousness has not been established because the combined references do not satisfy the requirement of disclosure of all claimed features. The argument has been considered but has not been found persuasive because of the reasons set forth above and in view of the new rejections. The rejection of claim 1 is proper and the rejection is maintained. Given that the rejection of claim 1 is proper, the Hemmila reference was set forth only to point out the conventional nature of FITC labeling. Applicant is again ignoring the teachings of the combined references. In view of the combined references, the claimed invention is obvious over the prior art.

8. Some of the Applicant's arguments are drawn to the rejection of claims 1 and 5 recited in the paper mailed September 15, 2005, pages 13-14, are relevant in the instant rejections.

Applicant argues that Strachan fails to disclose a method of calculating the activity of CDK as instantly claimed, thus a *prima facie* case of obviousness has not been established because the combined references do not satisfy the requirement of disclosure of all claimed features. Applicant argues that Strachan does not meet the

requisite level of motivation and reasonable expectation of success. The argument has been considered but has not been found persuasive because of the reasons set forth above and in view of the new rejections. The rejection of claim 1 is proper and the rejection is maintained. Given that the rejection of claim 1 is proper, the Strachan reference was set forth only to point out the conventional nature of peroxidase labeling. Applicant is again ignoring the teachings of the combined references. In view of the combined references, the claimed invention is obvious over the prior art.

9. All other rejections recited in the Office Action mailed 5/31/05 are hereby withdrawn.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

Susan Ungar, PhD
Primary Patent Examiner